There are three additional regulations that apply, although indirectly, to pesticides and reporting:

- EC Regulation 1185/2009 concerning statistics on pesticides requires that Member States shall collect data on pesticide sales and uses according to a harmonised format. The statistics on the placing on the market shall be transmitted yearly to the Commission and the statistics on agricultural use shall be transmitted every 5 year.
- Article 50 of Regulation (EC) 178/2002, laying down the general principles and requirements of food law, set up an improved and broadened rapid alert system covering food and feed (RASFF). The system is managed by the Commission and includes as members of the network Member States, the Commission and the Authority. It reports on non-authorised occurrences of pesticides residues and food poisoning cases.
- Article 45 (4) of EC Regulation 1272/2008 (CLP Regulation): importers and downstream users placing hazardous chemical mixtures on the market of an EU Member State will have to submit a notification to the Appointed Body/Poison Centre of that Member State. The notification needs to contain certain information on the chemical mixture, such as the chemical composition and toxicological information, as well as the product category to which the mixture belongs. The inclusion of information on the product category in a notification allows Appointed Bodies/Poison Centres to carry out comparable statistical analysis (e.g. to define risk management measures), to fulfil reporting obligations and to exchange information among MS. The product category is therefore not used for the actual emergency health response as such, but allows the identification of exposure or poisoning trends and of possible measures to prevent future poisoning cases. When formally adopted, the new Regulation will apply as of 1st January 2020.

While there are substantial legislative provisions, to this date a single unified EU "phytopharmacovigilance"[11] system akin to the pharmacovigilance system does not exist for PPP. Rather, a number of alerting systems have been developed within the EU to alert, notify, report and share information on chemical hazards that may pose a risk to public health in Member States. These systems cover different sectors including medicines, food stuffs, consumer products, industrial accidents, notifications under International Health Regulations (IHR) and events detected by EU Poisons Centres and Public Health Authorities. Each of these systems notify and distribute timely warnings to competent authorities, public organizations, governments, regulatory authorities and public health officials to enable them to take effective action to minimize and manage the risk to public health (Orford et al., 2014).

In the EU, information on acute pesticide exposure/incident originates mainly from data collected and reported by Poison Control Centres (PCC's). PCC's collect both cases of acute and chronic exposure/poisoning they are aware of, in the general population and in occupational settings. Cases are usually well-documented and information includes circumstances of exposure/incident, description of the suspected causal agent, level and duration of exposure, the clinical course and treatment and an assessment of the causal relationship. In severe cases, the toxin and/or the metabolites are usually measured in blood or urine. However, follow-up of cases reported to the centres merits further attention to identify potential long-term protracted effects.

There are two key obstacles to using Poison Centres data: official reports from national Poisons Centres are not always publicly available and when they are, there is a large heterogeneity in the format of data collections and coding, and assessment of the causal relationship. Indeed, each Member State has developed its own tools for collection activities resulting in difficulties for comparing and exchanging exposure data. In 2012, the European Commission funded a collaborative research and development project to support the European response to emerging chemical events: the Alerting and Reporting System for Chemical Health Threats, Phase III (ASHTIII) project. Among the various tools and methodologies that were considered, methods to exchange and compare exposure data from European PCC's were developed. As a feasibility study, work-package 5 included the development of a harmonized and robust coding system to enable Member States to compare

11 "phytovigilance" would refer to a vigilance system for plants; as pesticides are intended to be "medicines" for crops the term "phytopharmacovigilance" is considered to be the more appropriate one here. Furthermore it is a broad term used in France covering soil, water, air, environment, animal data, etc.

pesticide exposure data. However, results of a consultation with the PCC community showed that further coordination of data coding and collection activities is supported. It was concluded that more support and coordination is required at the EU and Member States level so that exposures data can be compared between Member States (Orford et al., 2015).

In addition to data collected by PCC's, several Member States have set up programs dedicated to occupational health surveillance[12]. The purpose of these programs is to identify the kinds of jobs, types of circumstances and pesticides that cause health problems in workers in order to learn more about occupational pesticide illnesses and injuries and how to prevent them. They are based on voluntary event notification by physicians (sometimes self-reporting by users) of any case of suspected work-related pesticide injury or illness or poisoning. In addition to medical data, information gathered includes data regarding type of crop, mode of application, temperature, wind speed, wearing of personal protection equipment, etc. Once collected, these data are examined and a report is released periodically; they provide a useful support to evaluate the safety of the products under re-registration. These data also highlight emerging problems and allow definition of evidence-based preventive measures for policy-makers. At EU level, the European Agency for Safety and Health at Work (EU-OSHA)[13] has very little in the way of monitoring of occupational pesticide-related illnesses data. In the USA, a programme specifically dedicated to pesticides funded and administered by the National Institute for Occupational Safety and Health (NIOSH) is in operation in a number of States[14]

In summary, currently human data may be collected in the form of case reports or case series, poison centres information, coroner's court findings, occupational health surveillance programmes or post marketing surveillance programmes. However, not all this information is present in the medical data submitted by applicants.

> Data collected through occupational health surveillance of the plant production workers or if they do so, the medical data are quite limited being typically basic clinical blood measurements, physical examinations, potentially with simple indications of how and where exposed took place, and there usually is no long term follow up. Furthermore, worker exposures in modern plants (especially in the EU) are commonly very low, and often their potential exposure is to a variety of pesticides (unless it is a facility dedicated to a specific chemical).

> Moreover, the reporting of data from occupational exposure to the active substances during manufacture is often combined with results from observations arising from contact with the formulated plant protection product as the latter information results from case reports on poisoning incidents and epidemiological studies of those exposed as a result of PPP use. Indeed, the presence of co-formulants in a plant protection product can modify the acute toxicological profile. Thus, to facilitate proper assessment, when reporting findings collected in humans it should be clearly specified whether it refers to the active substance per se or a PPP.

With regard to the requirements of specific data on diagnoses of poisoning by the active substance or formulated plant protection products and proposed treatments, which are also part of chapter 5.9 of the EC Regulation 283/2013, information is often missing or limited to those cases where the toxic mode of action is known to occur in humans and a specific antidote has been identified.

5.3. Proposals for improvement of current framework of case incident reporting

In order to avoid duplication and waste of effort, a logical next step would be to now develop, with all concerned public and private sector actors, an EU "phytopharmacovigilance" system for chemicals similar to the ones that have been put in place for medicines. In fact, while much experience has already been gained on how to gradually build such a system, it is nevertheless envisioned that this will take a number of years to be put in place.

[12] For example: Phyt'attitude in France is a vigilance programme developed by the Mutualité Sociale Agricole: http://www.msa.fr/lfr/sst/phyt-attitude

[13] https://osha.europa.eu/en/about-eu-osha

[14] SENSOR programme: https://www.cdc.gov/niosh/topics/pesticides/overview.html

Such a system may not merit being established solely for chemicals that are (predominantly) used as pesticides. However, given the legislative provisions already in place for pesticides, its development may need to be prioritised for pesticides.

In conclusion, European Commission together with the Member States should initiate the development of an EU-wide vigilance framework for pesticides. These should include:

- harmonization of human incident data collection activities at the EU level;
- coordination of the compilation of EU-wide databases;
- improving the collaboration between Poison Centres and regulatory authorities at national level in order to collect all the PPP poisonings produced in each Member State;
- guidance document on monitoring the impact of pesticide use on human health with harmonization of data assessment for causal relationships; and
- regular EU-wide reports.

6. Proposed use of epidemiological studies and vigilance data in support of the risk assessment of pesticides

This chapter briefly reviews the risk assessment process (section 6.1) based on experimental studies and discusses what information epidemiological studies could add to that process. Next, the assessment of the reliability of epidemiological studies is addressed in section 6.2. In section 6.3 the relevance of one or more studies found to be reliable is assessed.

6.1. The risk assessment process

Risk assessment is the process of evaluating risks to humans and the environment from chemicals or other contaminants and agents that can adversely affect health. For regulatory purposes the process used to inform risk managers consists of four steps (EFSA, 2012). On the one hand, information is gathered on the nature of toxic effects (hazard identification) and the possible dose-response relationships between the pesticide and the toxic effects (hazard characterisation). On the other hand, information is sought about the potential exposure of humans (consumers, applicators, workers, bystanders and residents) and of the environment (exposure assessment). These two elements are weighed in the risk characterisation to estimate that populations be potentially exposed to quantities exceeding the reference dose values, that is, to estimate the extra risk of impaired health in the exposed populations. Classically this is used to inform risk managers for regulatory purposes.

a) Step 1. *Hazard identification.*

Epidemiological studies and vigilance data are relevant for hazard identification as they can point to potential link between pesticide exposure and health. In this context epidemiological data can provide invaluable information in "scanning the horizon" for effects not picked up in experimental models. Importantly these studies also provide information about potentially enhanced risks for vulnerable population subgroups, sensitive parts of the lifespan, and gender selective effects.

b) Step 2. *Hazard characterisation* (Dose-Response assessment). As previously discussed a classic dose-response framework is not normally considered when using epidemiological data as the exposure dose is not assigned. The challenge presented when high quality epidemiological studies are available is to see whether these can best be integrated into the scheme as numerical input. A dose-response framework is rarely considered when using epidemiological data for risk assessment of pesticides. However, previous scientific opinions of the EFSA CONTAM Panel have used epidemiology as basis for setting reference values, particularly in the case of cadmium, lead, arsenic and mercury, which are the most well-known and data rich (EFSA 2009 a,b; EFSA 2010 b; EFSA 2012 b).Even when they may not form the basis of a dose-response assessment, vigilance and epidemiological data may provide supportive evidence to validate or invalidate a dose-response study carried out in laboratory animals. Characterisation of the relationships between varying doses of a chemical and incidences of adverse

effects in exposed populations requires characterisation of exposure or dose, assessment of response and selection of a dose-response model to fit the observed data in order to find a no-effect level. This raises two questions: can a dose-response be derived from epidemiological data to identify a no-effect level. If not, can epidemiological information otherwise contribute to the hazard characterisation?

Understanding dose-response relationships could also be relevant where adverse health outcomes are demonstrated to be associated with uses with higher exposures than EU good plant protection practice would give rise to, but where no association is observed from uses with lower exposures. It is clear that in this context the statistical summary of an epidemiological study defining RR or OR is potentially useful quantitative information to feed into the hazard characterisation process, when the study design meets the necessary standards.

c) Step 3. *Exposure assessment*. Data concerning the assessment of exposure are often hard to estimate in complex situations where a variety of uncontrolled "real-world" factors confound the analysis. As discussed previously, contemporary biological monitoring is rarely carried out in the general human population for practical reasons including high cost, test availability and logistics. However, it is anticipated that in the near future biomonitoring studies and data on quantitative exposure to pesticides will increase.

Step 4. *Risk characterisation*. In this final step, data on exposure are compared with health-based reference values to estimate the extra risk of impaired health in the exposed populations. Human data can indeed help verify the validity of estimations made based on extrapolation from the full toxicological database regarding target organs, dose-response relationships and the reversibility of toxic effects, and to provide reassurance on the extrapolation process without direct effects on the definition of reference values (London et al., 2010).

Epidemiological data might also be considered in the context of UFs. An UF of 10 is generally used on animal data to account for interspecies variability of effects and this is combined with a further factor of 10 to account for variation in susceptibility of different parts of the human population. However there are cases where only human data are considered (when this is more critical than animals data) and a single factor of 10 for intraspecies variability will apply. It is noted that at this moment Regulation (EC) No 1107/2009 Article 4(6) stipulates that: "In relation to human health, no data collected on humans shall be used to lower the safety margins resulting from tests on animals". The implication of this is that currently for risk assessment epidemiological data may only be used to increase the level of precaution used in the risk assessment, and not to decrease UFs even where relevant human data are available.

6.2. Assessment of the reliability of individual epidemiological studies

Factors to be considered in determining how epidemiology should be considered for a WoE assessment are described below and have been extensively outlined by available risk of bias tools for observational epidemiological studies (https://www.ncbi.nlm.nih.gov/books/NBK154464/ and Cochrane handbook). The following examples represent factors to look for not an exhaustive list:

Study design and conduct. Was the study design appropriate to account for the expected distributions of the exposure and outcome, and population at risk? Was the study conducted primarily in a hypothesis generating or a hypothesis-testing mode?

Population. Did the study sample the individuals of interest from a well-defined population? Did the study have adequate statistical power and precision to detect meaningful differences for outcomes between exposed and unexposed groups?

Exposure assessment. Were the methods used for assessing exposure valid, reliable and adequate? Was a wide range of exposures examined? Was exposure assessed at quantitative level or in a categorical or dichotomous (e.g. ever versus never) manner? Was exposure assessed prospectively or retrospectively?

Outcome assessment. Were the methods used for assessing outcomes valid, reliable and adequate? Was a standardized procedure used for collecting data on health outcomes? Were health outcomes ascertained independently from exposure status to avoid information bias?

Confounder control: were potential confounding factors appropriately identified? Were the methods used to document these factors valid, reliable and adequate?

Statistical analysis. Did the study estimate quantitatively the independent effect of an exposure on a health outcome of interest? Were confounding factors appropriately controlled in the analyses of the data?

Is the *reporting* of the study adequate and following the principles of the STROBE statement (or similar tools)?

The nature and the specificity of the outcome with regards to other known risk factors can influence the evaluation of human data for risk assessment purposes, particularly in case of complex health endpoints such as chronic effects with long induction and latency periods.

Study evaluation should provide an indication on the nature of the potential biases each specific study may have and an assessment of overall confidence in the epidemiological database. Table 2 shows the main parameters to be evaluated in single epidemiological studies and the associated weight (low, medium, high) for each parameter. Specific scientific considerations should be applied on a case-by-case basis, but it would be unrealistic to implement these criteria in a rigid and unambiguous manner.

Table 2. Study quality considerations for weighting epidemiological observational studies [15]

Parameter	High	Moderate	Low
Study design and conduct	Prospective studies. Pre-specified hypothesis (compound and outcome specific).	Case-control studies or prospective studies not adequately covering exposure or outcome assessment	Cross-sectional, ecological studies. Case-control studies not adequately covering exposure or outcome assessment
Population	Random sampling. Sample size large enough to warrant sufficient power Population characteristics well defined (including vulnerable subgroups)	Questionable study power, not justified in detail. Non-representative sample of the target population. Population characteristics not sufficiently defined	No detailed information on how the study population was selected. Population characteristics poorly defined
Exposure assessment	Accurate and precise quantitative exposure assessment (human biomonitoring or external exposure). Adequate assessment of exposure, preferentially biomarker concentrations at individual level. Validated questionnaire and/or interview for chemical-specific exposure answered by	Non-valid surrogate or biomarker in a specified matrix and external exposure. Questionnaire and/or interview for chemical-specific exposure answered by subjects or proxy individuals	Poor surrogate Low-quality questionnaire and/or interview; information collected for groups of chemicals. No chemical-specific exposure information collected; ever/never use of pesticides in general evaluated

[15] Adapted from US EPA (2016), based in turn on Munoz-Quezada et al. (2013) and LaKind et al. (2014)